UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

April 12, 2013

Kristina C. Borror, PhD
Director, Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

RE: Suspension of IRB Approval

University of Illinois at Chicago Research Protocol # 2009-1022
"Developing Brain Function in Adolescent Bipolar Disorder"
Sponsor: National Institute of Mental Health; Grant #5 R01 MH085639-04
Principal Investigator: Mani Pavuluri, MD

University of Illinois at Chicago Research Protocol # 2011-0654
"Brain Networks Modulating Affect Self-Regulation in Pediatric Mania"
Sponsor: National Institute of Mental Health; Grant #5 K24 MH09601116-02
Principal Investigator: Mani Pavuluri, MD

Dear Dr. Borror:

This communication is to inform you of the suspension of IRB approval for University of Illinois at Chicago (UIC) protocols 2009-1022, "Developing Brain Function in Adolescent Bipolar Disorder," and 2011-0654, "Brain Networks Modulating Affect Self-Regulation in Pediatric Mania," for which Dr. Mani Pavuluri, Professor and Director of the Pediatric Mood Disorders Clinic at UIC, is the Principal Investigator. Both of these studies were previously determined by the IRB to be not greater than minimal risk.

These protocols are being suspended as part of the corrective actions outlined in my April 8, 2013 letter. The April 8th letter informed OHRP of the UIC Institutional Review Board #1 (IRB00000115) determination of Serious Non-Compliance for the protocol "Affective Neuroscience of Pediatric Bipolar Disorder" (UIC protocol 2008-0624; NIMH Grant #5 R01 MH081019), and outlined the resulting corrective action plan. One of these corrective actions involved the suspension of greater than minimal risk and minimal risk human subject research studies where Dr. Pavuluri serves as Principal Investigator until her clinical research privileges

are restored (i.e., a minimum of 6 months). In the suspension letter to Dr. Pavuluri, she was asked to provide the IRB with: total number of enrolled subjects, number of active subjects, and, if applicable, the number of subjects, and a justification, as to who may need to continue the research for safety reasons.

Issues related to the previous non-compliance concerns will continue to be addressed per the corrective action plan as outlined in my April 8, 2013 letter. I will continue to you update you on our progress.

If you have any questions, please contact me at (312) 413-8731 or jfischer@uic.edu.

Sincerely,

James H. Fischer, PharmD
Director, Office for the Protection of Research Subjects
Human Protections Administrator, Office for the Vice Chancellor for Research
Executive Chair, UIC IRB
FWA #00000083

cc: Mitra Dutta, PhD, Vice Chancellor for Research
Clyde Wheeler, PhD, Associate Director, Investigator Outreach and Quality Improvement
Barbara Corpus, CIP, Associate Director, External Relations and Quality Assurance
Patricia West-Thielke, PharmD, Chair, IRB #1
Dmitri Azar, MD, Dean, College of Medicine
Anand Kumar, MD, Head, Department of Psychiatry
Mani Pavuluri, MD, Principal Investigator
Marjorie A. Garvey, Program Officer, National Institute of Mental Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of Mental Health
6001 Executive Boulevard
Bethesda, Maryland 20892

April 23, 2013

James H. Fischer, PharmD
Director
Office for the Protection of Research Subjects
Office of the Vice Chancellor for Research M/C 672
University of Illinois at Chicago
203 Administrative Office Building
1737 West Polk Street
Chicago, IL 60612-7227

Re: Acknowledgement of Determination of Serious Non-Compliance for R01MH081019 (Affective Neuroscience of Pediatric Bipolar Disorder); Principal Investigator: Mani Pavuluri, MD, PhD

Dear Dr. Fischer:

Thank you for your follow up letters of March 22, 2013 and April 8, 2013 regarding the report of serious non-compliance to the Office of Human Research Protection (OHRP) on the above-referenced grant. The NIMH commends the University of Illinois, Chicago (UIC) on its continued commitment to the protection of human research participants evidenced by the timely reporting of the internal audit findings to the OHRP and NIMH.

NIMH staff members have had an opportunity to review the information and evaluate the proposed corrective action plan. In the spirit of contributing to the robust corrective action plan already underway, NIMH wishes to draw attention to and request additional information on the following items:

1) NIMH seeks an evaluation of the full scale of the reported serious non-compliance in the R01MH081019 study. How many subjects participated in the non-IRB approved medication washout? How many participants failed to meet the IRB-approved inclusion/exclusion criteria at study entry? How many children younger than age twelve were administered off-label lithium as part of their study participation, and what were their respective ages? Did any of the under-twelve-aged participants experience a serious adverse event attributable to the study drug? Please provide assurance that appropriate clinical care was provided, as warranted.

2) Regarding the off-label administration of lithium to participants younger than age twelve in R01MH081019, did the UIC IRB determine whether an Investigational New Drug Application (IND) should have been filed with the Food and Drug Administration (FDA) or if the study was IND Exempt? If the UIC finds that a lapse of compliance occurred with FDA regulations (21 CFR Part 312), the NIMH asks to be informed of any corresponding notification to the FDA and study subjects.

3) A report from the R01MH081019 Data and Safety Monitoring Board, dated May 14, 2012, accompanied the March 22, 2013 consolidated letter of response from the Principal Investigator and the UIC. The NIMH notes that the DSMB constituted for this study included the Principal Investigator and a co-Investigator, and the DSMB report was prepared by a member of the research staff. The NIH Policy for Data and Safety Monitoring (June 1998, NOT-98-084) recommends that "participants involved in monitoring outcomes of a trial are in no way associated with the trial". The current UIC guidance on data and safety monitoring plans/boards/ committees (version 1.2, 3/30/12) references NOT-98-084. The NIMH strongly encourages the UIC to address this important issue in institutional guidance and training provided to UIC Institutional Review Boards that oversee NIH-supported research.

4) The April 8, 2013 report of serious non-compliance indicates that the head of the UIC Department of Psychiatry will develop a Standard Operating Procedure (SOP) establishing a process to ensure a clear distinction between clinical and research activities. The NIMH strongly recommends that this SOP address the distinct roles of clinician and researcher with regard to recruitment and consent activities.

5) The April 8, 2013 report of serious non-compliance also indicates that "Dr. Pavuluri must be removed as Principal Investigator from all research protocols." Have the research protocols and projects associated with, Dr. Pavuluri's two other NIMH grants—R01MH85639-04 and K24MH096011-02—been evaluated for noncompliance and, if so, were there any findings? (A separate letter is being sent to Mr. Luis Vargas, Executive Direct to determine the current status of each Dr. Pavuluri's grants.)

6) The March 22, 2013 report to OHRP indicates that the UIC will initiate an audit of studies overseen by IRB #1 to ensure compliance with 45 CFR Part 46.116 (required elements of informed consent). Please notify the NIMH of subsequent findings associated with this audit and any other official communication to or from the OHRP pertaining to the corrective action plans outlined in the March 22, 2013 or April 8, 2013 reports of serious non-compliance.

Thank you for your attention to this important matter. I ask for your response by May 23, 2013 which should be signed by the UIC's Authorized Organization Representative. Please feel free to contact me should you have any further questions or concerns.

Sincerely,

Rebecca D. Claycamp

Rebecca D. Claycamp, M.S., CRA
Chief Grants Management Officer
National Institute of Mental Health

cc: Mitta Dutta, Ph.D., Vice Chancellor for Research
Mani Pavuluri, MD, Principal Investigator
Teresa D. Johnston, Office for the Protection of Research Subjects
Marjorie A. Garvey, Program Officer, NIMH
Jane Steinberg, Ph.D., Director of the Division of Extramural Activities, NIMH
Christine Moretto, Human Subjects Projection Administrator, NIMH

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of Mental Health
6001 Executive Boulevard
Bethesda, Maryland 20892

April 23, 2013

Mr. Luis Vargas
Executive Director
Office of Research Services
Office of the Vice Chancellor for Research
University of Illinois at Chicago
310 Administrative Office Building, M/C 672
1737 West Polk Street
Chicago, IL 60612-7227

Re: Status of NIMH grants for Mani Pavuluri, MD, PhD
5R01MH81019-05 *Affective Neuroscience of Pediatric Bipolar Disorder*
5R01MH85639-04 *Developing Brain Function in Adolescent Bipolar Disorder*
5K24MH96011-02 *Brain Networks Modulating Affect Self-Regulation in Pediatric Mania*

Dear Mr. Vargas:

As you are likely aware, the University of Illinois Chicago recently made a determination of serious non-compliance for R01MH81019 reported to the Office of Human Research Protection (OHRP) and the National Institute of Mental Health (NIMH) in an initial report on March 22, 2013 and a follow-up report on April 8, 2013. The NIMH commends the University's timely action on reporting the matter and commitment to working the NIMH and OHRP to put corrective actions in place. In the April 8 report the University indicated that "Dr. Pavuluri must be removed as Principal Investigator from all research protocols", and indicated plans for appointing "caretaker" Principal Investigator to the grants. NIMH writes to discuss our expectations for the three grants.

Appointing a "caretaker" PI for more than three months does require an official prior approval request for change of PI following procedures outlined in the NIH Grants Policy Statement. Requests should be directed to the grants specialist named in the eRA Commons: currently Carmen Herbert (MH81019) or Jackie Chia (R01MH085639).

We have particular concern regarding the K24. As the grant is non-transferable, we do not see how the grant can continue while Dr. Pavuluri is effectively barred from human subjects research for six months up to a year; therefore, this grant is hereby suspended. All work must be suspended and no further funds may be expended from this grant, pending resolution as described below.

NIMH
National Institute of Mental Health

For the grant to be reinstated, the University must in writing to propose how the institution envisions progress on this award. The letter must be signed by the principal investigator by the institutional authorized official and must be postmarked no later than May 23 (In the interest of expediency, correspondence may be sent as a pdf attachment to an email.) Should a case be made for reinstatement, those costs that the IC will allow for the period of the suspension will be determined by the GMO in consultation with the PO. If the case for continuation has not been made during that time frame, the NIMH will move to consider further enforcement actions.

Given the situation, the University of Illinois Chicago may elect on its own accord to terminate the grant. If that is the institution's desire, the institution may reply in writing, referencing the identified grant with a letter signed by the principal investigator and the institutional authorizing official. This letter can be sent as a pdf attachment to an email.

Please contact me if you have questions or concerns regarding any point of this process.

Sincerely,

Rebecca D. Claycamp

Rebecca D. Claycamp, M.S., CRA
Chief Grants Management Officer
National Institute of Mental Health

cc: Mitta Dutta, Ph.D., Vice Chancellor for Research
Mani Pavuluri, MD, Principal Investigator
Marjorie A. Garvey, Ph.D., Program Officer, NIMH
Shelli Avenevoli, Ph.D., Program Officer, NIMH
Jane Steinberg, Ph.D., Director of the Division of Extramural Activities, NIMH
Diane Dean, Director, Office of Compliance, NIH-OPERA

UIC UNIVERSITY OF ILLINOIS AT CHICAGO

Office of the Vice Chancellor for Research (MC 672)
310 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612

May 22, 2013

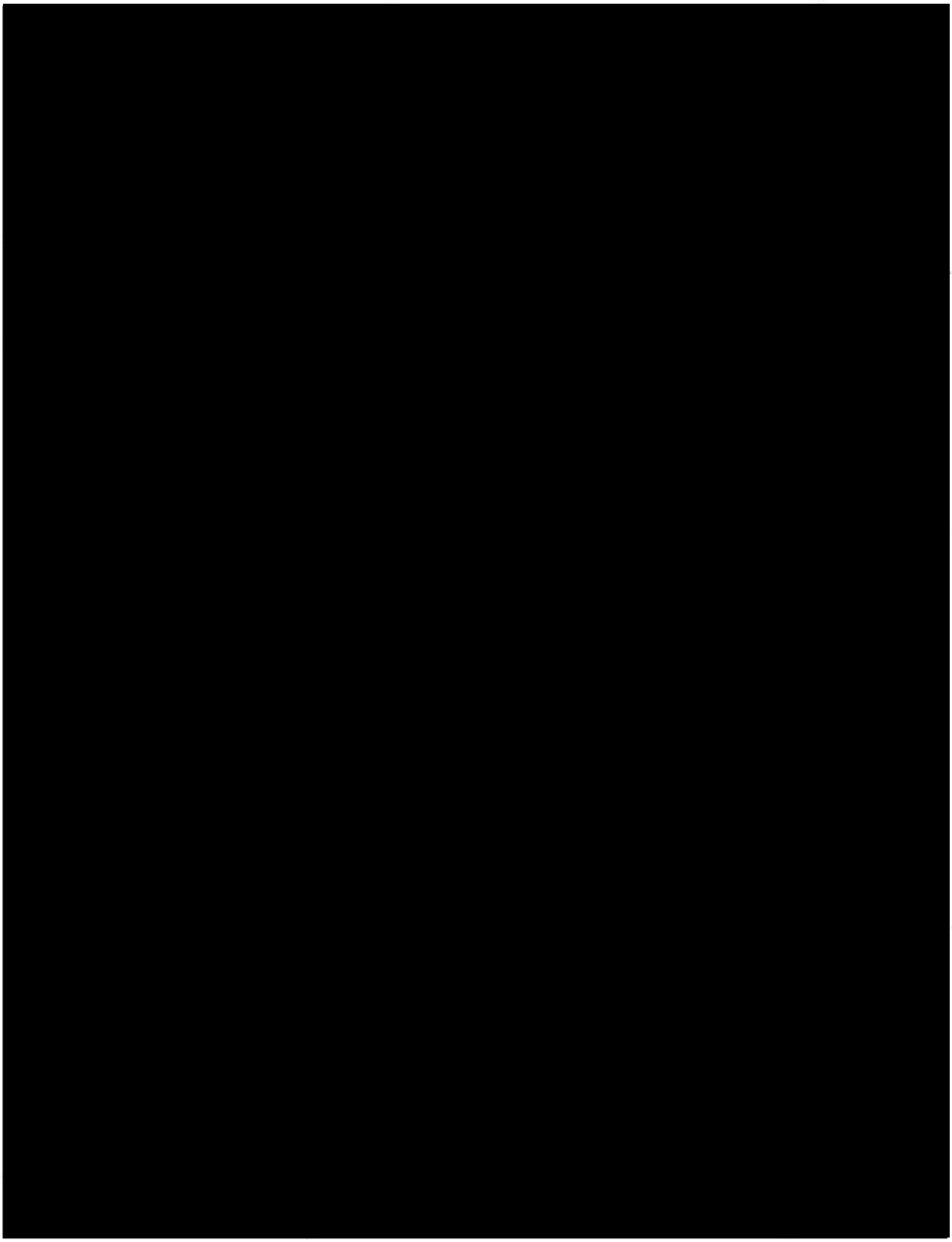
Rebecca Claycamp, M.S., CRA
Chief Grants Management Officer
National Institute of Mental Health
6001 Executive Boulevard
Bethesda, MD 20892

RE: Response to April 23, 2013 NIMH Inquiry for R01MH081019 (Affective Neuroscience of Pediatric Bipolar Disorder); Principal Investigator: Mani Pavuluri, MD, PhD

Dear Ms. Claycamp:

Thank you for providing the University of Illinois at Chicago (UIC) the opportunity to respond to the issues NIHM raised regarding Dr. Pavuluri's research. It is hoped that the Agency will find the actions taken to date to be satisfactory and reflective of our Institution's commitment regarding the protection of human subjects participating in research at UIC.

[redacted]



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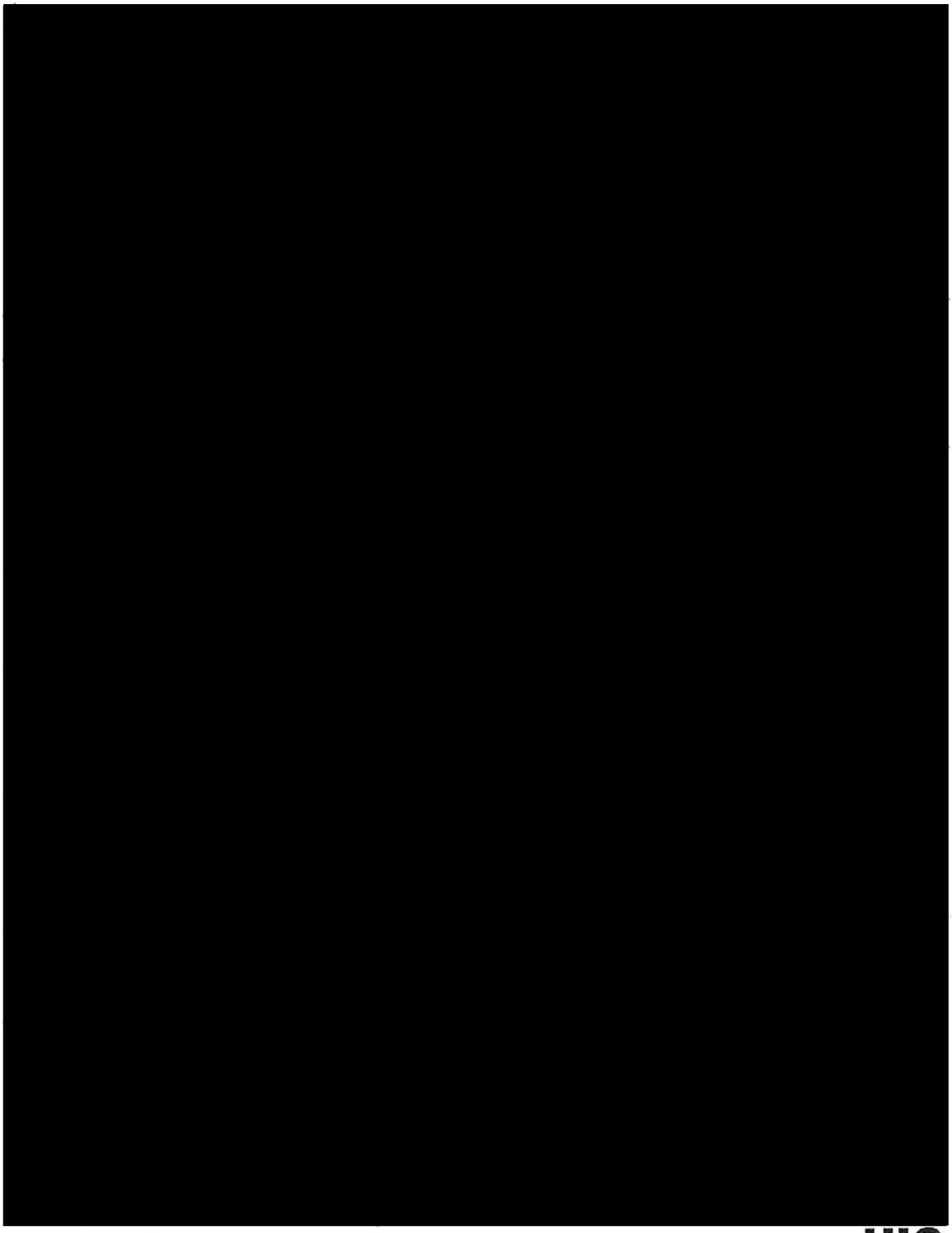
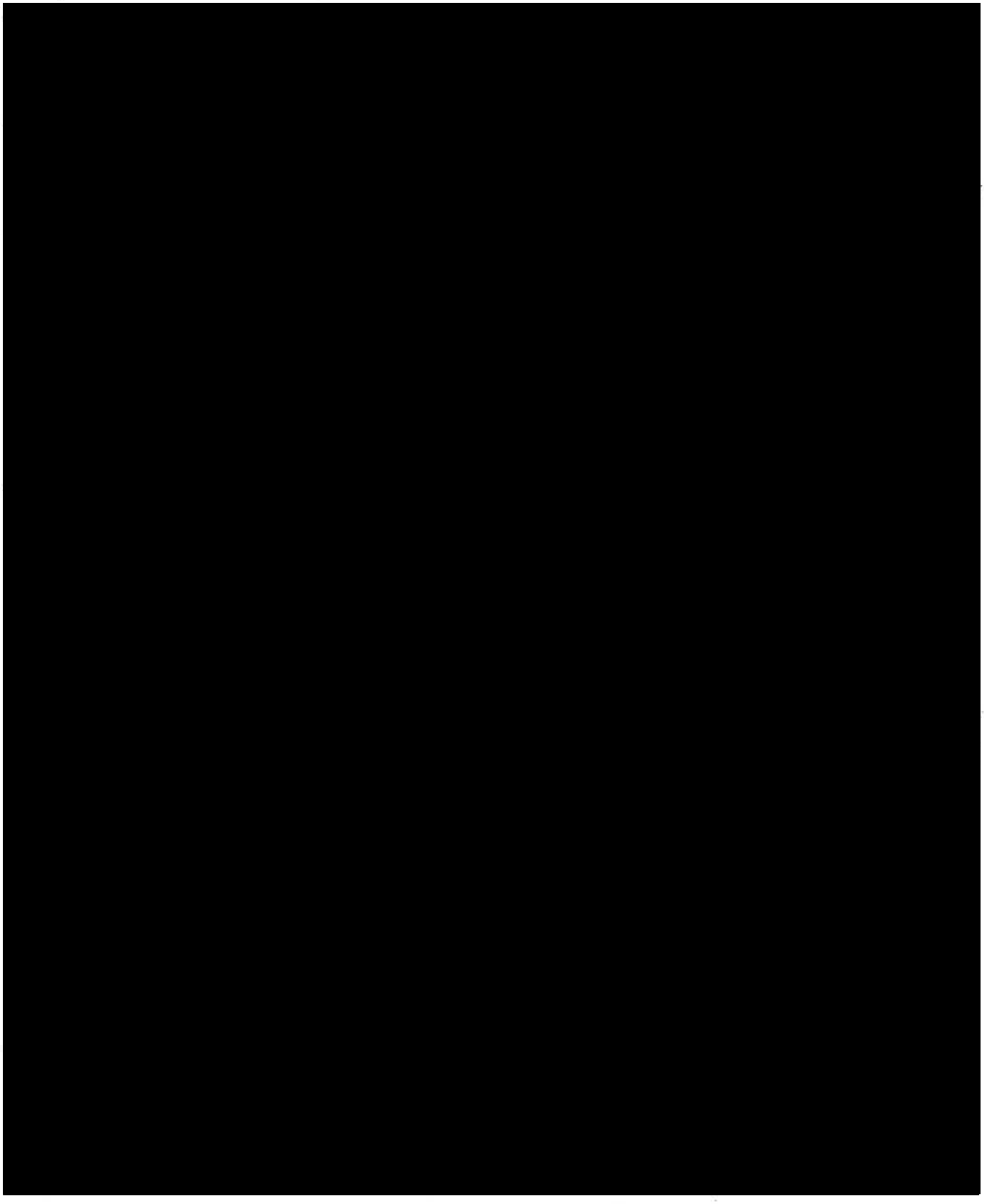


UIC



UIC

Sincerely,

James H. Fischer, PharmD
Director, Office for the Protection
of Research Subjects
Human Protections Administrator
FWA #00000083

Mitra Dutta, PhD
Vice Chancellor for Research
UIC Distinguished Professor, Department of
Electrical and Computer Engineering

cc: Patricia West-Thielke, PharmD, Chair, IRB #1
Dimitri Azar, MD, Dean, College of Medicine
Anand Kumar, MD, Head, Department of Psychiatry
Mani Pavuluri, MD, Principal Investigator

Attachments: Follow-up Letter to OHRP regarding IRB #1 Serious Non-Compliance, dated May 16, 2013

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June 11, 2013

Kristina C. Borror, PhD
Director, Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

RE: Determination of Serious and Continuing Non-Compliance

University of Illinois at Chicago Research Protocol # 2011-0654
"Brain Networks Modulating Affect Self-Regulation in Pediatric Mania"
Sponsor: National Institute of Mental Health; Grant #5 K24 MH096011-02
Principal Investigator: Mani Pavuluri, MD

Dear Dr. Borror:

This communication is a follow-up related to the Suspension of IRB Approval for University of Illinois at Chicago (UIC) protocol 2011-0654, "Brain Networks Modulating Affect Self-Regulation in Pediatric Mania," as previously reported on April 12, 2013. Dr. Mani Pavuluri, Professor and Director of the Pediatric Mood Disorders Clinic at UIC, is the Principal Investigator.

In an April 23, 2013 letter from NIMH representatives regarding the follow-up of the audit results of Dr. Pavuluri's protocol 2008-0624 (Grant #R01MH081019), "Affective Neurosciences of Bipolar Disorder," an inquiry was made as to whether Dr. Pavuluri's other active NIMH grants and projects had been evaluated for non-compliance. The UIC Institutional Review Board (IRB) #1 had also requested an audit of Dr. Pavuluri's other human subject protocols during their review of Protocol 2008-0624. Consequently, the Office for the Protection of Research Subjects (OPRS) initiated an audit of this study.

The results of the audit were reviewed by the IRB #1 at the June 5, 2013 convened meeting. The audit was limited to those subjects enrolled with pediatric bipolar disorder (PBD). Records from all six (6) subjects with PBD enrolled in the research were reviewed.

The findings from the audit report included:

- **Failure to follow the eligibility criteria specified in the IRB approved protocol.** The investigator enrolled subjects who were outside the criteria approved by the IRB for participation in the study for one or more of the following criteria: age, medication exposure, specific bipolar disorder diagnosis, comorbid conditions, and current or history in past three

(3) months of a diagnosis of substance abuse/dependence, or use of illicit drugs or alcohol in past three (3) weeks

- **Failure to follow the IRB-approved protocol during the conduct of the study.** The auditors identified the performance of several assessments that were not included in the IRB-approved protocol, as well as the failure to perform some procedures described in the protocol. . In addition, research related procedures were conducted in subjects prior to the date of assent and parental/guardian permission.
- **Deficiencies in the Informed Consent and Assent documents.** These included use of invalid assent documents (e.g., not the currently approved version or not an approved version for a given age group; subject signed assent document in pencil; and some subjects' names were included on the first page of the assent document while the first page of the assent was blank for one subject.
- **Deficiencies/Irregularities in subject study files.** Several subjects in this study were co-enrolled in other protocols. As a result, data from another study, which may have been collected on a date prior to informed consent being obtained for the current study, was used to establish eligibility or as a baseline assessment of the subject's present status. In addition, the date recorded on the study's pregnancy log is the date consent was obtained; however, the date that the pregnancy test was performed is not indicated. Lastly, the pregnancy log is not ordered by date or by subject ID number.

The IRB determined that the findings described above represent Serious Non-Compliance, as they increase the potential risk of harm to the subjects' rights and welfare and compromise the integrity of the research data and the human subject protection program. The IRB further determined that findings represent Continuing Non-Compliance, as the deficiencies are similar to those identified for protocol 2008-0624.

The IRB has determined that Dr. Pavuluri is to complete the corrective action plan as outlined in my letter dated April 8, 2013. The current protocol remains Suspended at this time. I believe these issues are being appropriately addressed, and I will provide a follow-up report if the IRB makes any additional determinations or corrective actions related to this protocol.

If you have any questions, please contact me at (312) 413-8731 or jfischer@uic.edu.

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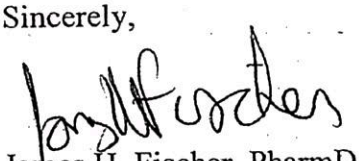

James H. Fischer, PharmD
Director, Office for the Protection of Research Subjects
Human Protections Administrator, Office for the Vice Chancellor for Research
Executive Chair, UIC IRB
FWA #00000083

cc: Mitra Dutta, PhD, Vice Chancellor for Research
Clyde Wheeler, PhD, Associate Director, Investigator Outreach and Quality Improvement
Barbara Corpus, CIP, Associate Director, External Relations and Quality Assurance
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Mani Pavuluri, MD, Principal Investigator
Marjorie A. Garvey, Program Officer, National Institute of Mental Health

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RE: Determination of Serious and Continuing Non-Compliance

University of Illinois at Chicago Research Protocol # 2009-1022
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Sponsor: National Institute of Mental Health; Grant #5 R01 MH085639-04
Principal Investigator: Mani Pavuluri, MD

Dear Dr. Borror:

This communication is a follow-up related to the Suspension of IRB Approval for University of Illinois at Chicago (UIC) protocol 2009-1022, "Developing Brain Function in Adolescent Bipolar Disorder," as previously reported on April 12, 2013. Dr. Mani Pavuluri, Professor and Director of the Pediatric Mood Disorders Clinic at UIC, is the Principal Investigator.

In an April 23, 2013 letter from NIMH representatives regarding the follow-up of the audit results of Dr. Pavuluri's protocol 2008-0624 (Grant #R01MH081019), "Affective Neurosciences of Bipolar Disorder," an inquiry was made as to whether Dr. Pavuluri's other active NIMH grants and projects had been evaluated for non-compliance. The UIC Institutional Review Board (IRB) #1 had also requested an audit of Dr. Pavuluri's other human subject protocols during their review of Protocol 2008-0624. Consequently, the Office for the Protection of Research Subjects (OPRS) initiated an audit of this study.

The results of the audit were reviewed by the IRB #1 at the June 5, 2013 convened meeting. The audit was limited to those subjects enrolled with pediatric bipolar disorder (PBD). Records from twenty-two (22) of the 129 children with PBD enrolled in the research were randomly selected for review

The findings from the audit report included:

- **Failure to follow the eligibility criteria specified in the IRB approved protocol.** The investigator enrolled subjects who were outside the criteria approved by the IRB for participation in the study for one or more of the following criteria: age, medication exposure, specific bipolar disorder diagnosis, comorbid conditions, and history of self-mutilation or suicidal behavior.

- **Failure to follow the IRB-approved protocol during the conduct of the study.** The auditors identified the performance of several assessments that were not included in the IRB-approved protocol, as well as the failure to perform some procedures described in the protocol. In addition, research related procedures were conducted in subjects prior to the date of assent and parental/guardian permission.
- **Deficiencies in the Informed Consent and Assent documents.** These included study informed consent binders containing two sets of documents for individual subjects without an explanation; inconsistencies between dates of obtaining assent and parental permission; inconsistency between the person obtaining assent and the person obtaining permission; corrections made in an improper manner (e.g., initials and date not provided to allow attribution); and some subjects' names were included on the first page of the assent document while some subjects' names were not included on the first page of the assent document.
- **Deficiencies/Irregularities in subject study files.** Several subjects in this study were co-enrolled in other protocols. As a result, data from another study, which may have been collected on a date prior to informed consent being obtained for the current study, was used to establish eligibility or as a baseline assessment of the subject's present status. In addition, the date recorded on the study's urine pregnancy testing log is the date consent was obtained; however, the date that the pregnancy test was performed is not indicated. Lastly, the pregnancy testing log is not ordered by date or by subject ID number.

The IRB determined that the findings described above represent Serious Non-Compliance, as they increase the potential risk of harm to the subjects' rights and welfare and compromise the integrity of the research data and the human subject protection program. The IRB further determined that findings represent Continuing Non-Compliance, as the deficiencies are similar to those identified for protocol 2008-0624.

The IRB has determined that Dr. Pavuluri is to complete the corrective action plan as outlined in my letter dated April 8, 2013. The current protocol remains Suspended at this time. I believe these issues are being appropriately addressed, and I will provide a follow-up report if the IRB makes any additional determinations or corrective actions related to this protocol.

If you have any questions, please contact me at (312) 413-8731 or jfischer@uic.edu.

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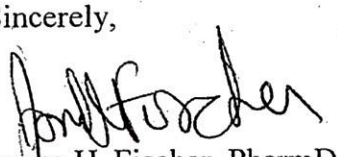

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